



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 862

[Docket No. FDA-2014-N-1112]

Medical Devices; Clinical Chemistry and Clinical Toxicology Devices; Classification of Hemoglobin A1c Test System

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying hemoglobin A1c test system into class II (special controls). The special controls that will apply to this device are identified in this order and will be part of the codified language for the hemoglobin A1c test system classification. The Agency is classifying the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device.

DATES: This order is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. The classification was applicable May 23, 2013.

FOR FURTHER INFORMATION CONTACT: Meshaun Payne, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5650, Silver Spring, MD 20993-0002, 301-796-6668.

SUPPLEMENTARY INFORMATION:

I. Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May

28, 1976 (the date of enactment of the Medical Device Amendments of 1976), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until the device is classified or reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1). Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, within 30 days of receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a classification under section 513(f)(2) of the FD&C Act. If the person submits a request to classify the device under this second procedure, FDA may decline to undertake the classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device

submitted is not of “low-moderate risk” or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA will classify the device by written order within 120 days. This classification will be the initial classification of the device.

In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on March 14, 2013, classifying the COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 assay into class III, because it was not substantially equivalent to a device that was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, or a device which was subsequently reclassified into class I or class II. On March 29, 2013, Roche Diagnostics Corporation submitted a request for classification of the COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 assay under section 513(f)(2) of the FD&C Act. The manufacturer recommended that the device be classified into class II.

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1). FDA classifies devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the de novo request, FDA determined that the device can be classified into class II with the establishment of special controls. FDA believes these special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on May 23, 2013, FDA issued an order to the requestor classifying the device into class II. FDA is codifying the classification of the device by adding § 862.1373.

Following the effective date of this final classification administrative order, any firm submitting a premarket notification (510(k)) for a hemoglobin A1c test system will need to comply with the special controls named in the final administrative order.

The device is assigned the generic name hemoglobin A1c test system, and it is identified as a device used to measure the percentage concentration of hemoglobin A1c in blood. Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of patients at risk for developing diabetes mellitus.

FDA has identified the following risks to health associated with this type of device and the measures required to mitigate these risks in table 1:

Table 1.--Identified Risks and Required Mitigations

Identified Risks	Required Mitigations
False negative result due to inadequate device performance	Special controls (1) and (2)
False positive result due to inadequate device performance	Special controls (1) and (2)
Use of the test for patients with hemoglobin variants that may interfere with the test system, and lead to incorrect results	Special control (3)

FDA believes that the following special controls, in addition to the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness:

1. The device must have initial and annual standardization verification by a certifying glycohemoglobin standardization organization deemed acceptable by FDA.

2. The premarket notification submission must include performance testing to evaluate precision, accuracy, linearity and interference, including the following:

- Performance testing of device precision must, at a minimum, use blood samples with concentrations near 5.0 percent, 6.5 percent, 8.0 percent and 12 percent hemoglobin A1c. This testing must evaluate precision over a minimum of 20 days using at least three lots of the device and three instruments, as applicable.
- Performance testing of device accuracy must include a minimum of 120 blood samples that span the measuring interval of the device and compare results of the new device to results of a standardized test method. Results must demonstrate little or no bias versus the standardized method.
- Total error of the new device must be evaluated using single measurements by the new device compared to results of the standardized test method, and this evaluation must demonstrate a total error less than or equal to 6 percent.
- Performance testing must demonstrate that there is little to no interference from common hemoglobin variants, including Hemoglobin C, Hemoglobin D, Hemoglobin E, Hemoglobin A2, and Hemoglobin S.

3. When assay interference from Hemoglobin F or interference with other hemoglobin variants with low frequency in the population is observed, a warning statement must be placed in a black box and must appear in all labeling material for these devices describing the interference and any affected populations.

Hemoglobin A1c test system devices are prescription devices restricted to patient use only upon the authorization of a practitioner licensed by law to administer or use the device. (See section 520(e) of the FD&C Act (21 U.S.C. 360j(e)) and 21 CFR 801.109 (Prescription

devices). Prescription-use restrictions are a type of general control as defined in section 513(a)(1)(A)(i) of the FD&C Act.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this type of device, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device. Therefore, this device type is not exempt from premarket notification requirements. Persons who intend to market this type of device must submit to FDA a premarket notification, prior to marketing the device, which contains information about the hemoglobin A1c test system they intend to market.

II. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

III. Paperwork Reduction Act of 1995

This final administrative order establishes special controls that refer to previously approved collections of information found in other FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820 have been approved under OMB control number 0910-0073; and the collections of information in 21 CFR

parts 801 and 809 regarding labeling have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 862

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 862 is amended as follows:

PART 862--CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES

1. The authority citation for 21 CFR part 862 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Add § 862.1373 to subpart B to read as follows:

§ 862.1373 Hemoglobin A1c test system.

(a) Identification. A hemoglobin A1c test system is a device used to measure the percentage concentration of hemoglobin A1c in blood. Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of patients at risk for developing diabetes mellitus.

(b) Classification. Class II (special controls). The special controls for this device are:

(1) The device must have initial and annual standardization verification by a certifying glycohemoglobin standardization organization deemed acceptable by FDA.

(2) The premarket notification submission must include performance testing to evaluate precision, accuracy, linearity, and interference, including the following:

(i) Performance testing of device precision must, at a minimum, use blood samples with concentrations near 5.0 percent, 6.5 percent, 8.0 percent, and 12 percent hemoglobin A1c. This

testing must evaluate precision over a minimum of 20 days using at least three lots of the device and three instruments, as applicable.

(ii) Performance testing of device accuracy must include a minimum of 120 blood samples that span the measuring interval of the device and compare results of the new device to results of a standardized test method. Results must demonstrate little or no bias versus the standardized method.

(iii) Total error of the new device must be evaluated using single measurements by the new device compared to results of the standardized test method, and this evaluation must demonstrate a total error less than or equal to 6 percent.

(iv) Performance testing must demonstrate that there is little to no interference from common hemoglobin variants, including Hemoglobin C, Hemoglobin D, Hemoglobin E, Hemoglobin A2, and Hemoglobin S.

(3) When assay interference from Hemoglobin F or interference with other hemoglobin variants with low frequency in the population is observed, a warning statement must be placed in a black box and must appear in all labeling material for these devices describing the interference and any affected populations.

Dated: August 19, 2014.

Peter Lurie,

Associate Commissioner for Policy and Planning.